University Code: 10384

Student ID No.: 20420131154522

MASTER OF SCIENCE DEGREE THESIS

Preparation and application of acidic ionic liquids in the synthesis of 7-hydroxy-4-methylcoumarin via the Pechmann-Duisberg condensation reaction

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Date of Graduation: June, 2015

A THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF ENGINEERING

DEPARTMENT OF CHEMICAL AND BIOCHEMICAL ENGINEERING

COLLEGE OF CHEMISTRY AND CHEMICAL ENGINEERING

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Certification

I, _____, hereby certify that I have read this manuscript and recommend it for acceptance by Xiamen University as a thesis entitled: "Preparation and application of acidic ionic liquids in the synthesis of 7-hydroxy-4-methylcoumarin via the Pechmann-Duisberg condensation reaction" in partial fulfilment of degree of Master of Engineering at Xiamen University, People's Republic of China.

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Original Statement

The research described in this Master of Engineering thesis was conducted under the supervision of Professor Sifang LI at the Department of Chemical and Biochemical Engineering, Xiamen University. I hereby declare that the work submitted is my own and that appropriate credit has been given where reference has been made to the work of others. I also confirm that it has not been previously or concurrently submitted for any other degree, diploma, or any other qualification at Xiamen University, P.R China, or any other institutions.

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Acknowledgements

I would like to extend my sincerest and humblest gratitude to the following people and organizations for the support they afforded me towards the development of this thesis:

First would be Prof. Li Sifang for accepting me in his laboratory and accommodating my presence or periodic absence therein, availing himself for constructive consultation whenever I needed it and for setting the general direction towards the final realization of this thesis. Without his unending patience, my experience through this project would not have been as comfortable and successful as it was.

Second in line is my labmate and colleague, Xiaoxia, without whom the acquisition of data for this thesis would not have been possible. It is through her guidance and training that this thesis came to fruition.

Third for consideration would be my coursemates, with special recognition to William Brown and Amir Makin, for their psychological and technical support that made the process of writing this thesis much more bearable than it would otherwise have been.

Also worthy of mention is the Xiamen University Chemical and Biochemical Engineering department for its accepting me into their department and overseeing my academic wellbeing throughout my study.

Lastly but by no means the least would be the Chinese government and Xiamen University, both for providing me the opportunity to study in an esteemed Chinese university in one of the most beautiful cities of China.

Abstract

7-hydroxy-4-methylcoumarin, or 4-methylumbelliferone, is a fluorescently active compound with numerous applications in various parts of human life. The Pechmann-Duisberg condensation reaction is commonly used to synthesize it because of the simplicity and economic feasibility of the reaction. Conventionally, corrosive, toxic and hazardous mineral acids are used to catalyze this reaction. In line with requirements for improvement of organic synthetic methods towards greater ecofriendliness, there is need to replace these catalysts with greener alternatives. In this study, three acidic ionic liquids, N-methyl-2-pyrrolidonium hydrogen sulphate, 1-methylimidazolium hydrogen sulphate and polyvinylpyrrolidonium hydrogen sulphate were synthesized and applied in the Pechmann-Duisberg reaction for the synthesis of 4-methylumbelliferone. Their respective performances in this reaction were compared against each other and against that of sulphuric acid on the basis of 4-methylumbelliferone yields produced. Their "green-ness" in the reaction was also assessed.

The maximum yields obtained for the three catalysts included 75% for polyvinylpyrrolidonium hydrogen sulphate, 64% for N-methyl-2-pyrrolidonium hydrogen sulphate and 64% for 1-methylimidazolium hydrogen sulphate. The yield of sulphuric acid was 52%. FT-IR characteristic peaks for polyvinylpyrrolidonium hydrogen sulphate were observed at 2962, 1643, 1288, 1069, 3392 and1174; those for N-methyl-2-pyrrolidonium hydrogen sulphate at 1696, 1069, 2926, 3385 and 1170 and; those for 1-methylimidazolium hydrogen sulphate at 3146, 2854, 840, 760, 3393 and 1191. From the Hammet acidity function test, the H_o values for 1-methylimidazolium hydrogen sulphate, N-methyl-2-pyrrolidonium hydrogen sulphate and sulphuric acid were determined to be 3.42, 1.54 and 1.31 respectively. Reaction mass efficiency values obtained were 44% for N-methyl-2-pyrrolidonium hydrogen sulphate, 48% for polyvinylpyrrolidonium hydrogen sulphate, 35% for 1-methylimidazolium hydrogen sulphate and 38% for sulphuric acid. From these results, and after comparing the effects of temperature and mole ratio on the performance of the three synthesized catalysts, it was concluded that even though polyvinylpyrrolidonium hydrogen sulphate generated the highest yields, N-methyl-2-pyrrolidonium hydrogen sulphate showed the best applicability in the reaction in terms of yield production, reaction conditions required for its performance, its "green-ness" and general ease of handling. 1-methylimidazolium hydrogen sulphate showed the worst applicability in this respect.

Keywords: 4-methylumbelliferone; Pechmann-Duisberg condensation; acidic ionic liquids

摘要

7-羟基-4-甲基香豆素（又名羟甲香豆素）大量应用于人类生活的各个方面。7-羟基-4-甲基香豆素最常用的合成方法是应用 Pechmann 缩合反应，该反应具有操作简单，产率较高等优点。传统的 7-羟基-4-甲基香豆素合成反应中使用的催化剂一般为无机酸，这些催化剂具有设备腐蚀性大，严重危害生态环境等缺点。在日益倡导绿色合成的今天，多种绿色催化剂已被应用于 7-羟基-4-甲基香豆素的合成研究中。本文主要研究 N-甲基吡咯烷酮硫酸氢盐、N-甲基咪唑硫酸氢盐、聚乙烯基吡咯烷酮硫酸氢盐这三种离子液体的制备以及将这三种不同的离子液体应用到 Pechmann 缩合反应催化合成 7-羟基-4-甲基香豆素。由 7-羟基-4-甲基香豆素的收率比较这三种离子液体催化剂和硫酸在反应中的催化效果并运用绿色指标对反应进行评估。

由以上三种离子液体和硫酸作为催化剂催化合成 7-羟基-4-甲基香豆素得到的最大收率如下：聚乙烯基吡咯烷酮硫酸氢盐为催化剂的收率为 75%；N-甲基吡咯烷酮硫酸氢盐作为催化剂的收率为 64%；N-甲基咪唑硫酸氢盐作为催化剂的收率为 64%；硫酸为催化剂的收率为 52%。聚乙烯基吡咯烷酮硫酸氢盐经过红外光谱(FT-IR）分析得出它的特征峰在 2962cm^{-1}, 1643 cm^{-1}, 1288 cm^{-1}, 1069 cm^{-1}, 3392 cm^{-1} 和 1174 cm^{-1}。运用绿色指标 Reaction mass efficiency 评估这三种离子液体的催化的反应，得到的结果为：N-甲基吡咯烷酮硫酸氢盐为 44%；聚乙烯基吡咯烷酮硫酸氢盐为 48%；N-甲基咪唑硫酸氢盐为 38%。通过 Hammet 法测定 N-甲基咪唑硫酸氢盐、N-甲基吡咯烷酮硫酸氢盐、和硫酸的酸度，得出它们的 H_0 分别为 3.42, 1.54，1.31。综合以上分析结果以及比较这三种离子液体的反应温度、反应物的摩尔比得出以聚乙烯基吡咯烷酮硫酸氢盐为催化剂所得的产率最高；虽然 N-甲基吡咯烷酮硫酸氢盐的收率虽比聚乙烯基吡咯烷酮硫酸氢盐的低，但是它的反应条件比较温和；而 N-甲基咪唑硫酸氢盐相对来效果不佳。

关键词：7-羟基-4-甲基香豆素；Pechmann 缩合反应；离子液体

Abbreviations

7h4mc	7-hydroxy-4-methylcoumarin
PD	Pechmann-Duisberg
4-MU	4-methylumbelliferone
NMP	N-methylpyrrolidonium
[HNMP]HSO_4	N-methyl-pyrrolidonium hydrogen sulphate
mim	1-methylimidazole
[Hmim]HSO_4	1-methyimidazolium hydrogen sulphate
[HPVP]HSO_4	Polyvinylpyrrolidonium hydrogen sulphate
H_2SO_4	Sulphuric acid
HCl	Hydrochloric acid
H_3PO_4	Phosphoric acid
$HClO_4$	Perchloric acid
[bmim][HSO_4]	1-butyl-3-methyl-imidazolium hydrogen sulphate
[MBsIm][CF_3SO_3]	1-methyl-3-(butyl-4-sulfonate)imidazolium triflate
[BMIm][H_2PO_4]	1-butyl-3-methyl-imidazolium hydrogen sulphate
[HMIm]BF_4	1-methylimidazolium tetrafluoroborate
[BSMIm]Ts	1-butanesulfonic acid-3-methylimidazolium tosylate
[Msim]HSO_4	3-methyl-1-sulfonic acid imidazolium hydrogen sulphate
[bmim]OH	1-butyl-3-methyl-imidazolium hydroxide
[bmim]Cl•2$AlCl_3$	1-butyl-3-methyl-imidazolium chloride trichloroaluminate
-SO_3	-sulphur trioxide

PVP	Polyvinylpyrrolidone
FT-IR	Fourier Transform Infrared Spectroscopy
HPA	Heteropolyacid
RME	Reaction mass efficiency
Res	Resorcinol
EAA	Ethyl acetoacetate
IUPAC	International Union of Pure and Applied Chemistry
BASF	Badische Anilin- und Soda-Fabrik (Company)
Cat:sub ratio	Catalyst:substrate mole ratio
SLP	Supported Liquid Phase
SAP	Supported Aqueous Phase
SILPs	Supported Ionic Liquids Phases
APIs	Active Pharmaceutical Ingredients
CAS	Chemical Abstracts Service

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Chapter 1 Introduction and literature review

7-hydroxy-4-methylcoumarin (also known as 4-methylumbelliferone) is a technologically valuable chemical whose application cuts across the physical and biological sciences. From the pharmaceutical industry to laser technology, this chemical has been studied and applied in numerous areas and instances throughout the years since its laboratory synthesis in the 19th century. Although limited information exists in open literature on its current commercial value, the information that is there clusters it with other coumarins and these are in turn clustered under the 100 billion dollar fine chemical industry [1, 2].

Among the methods available for its production [3], the Pechmann-Duisberg condensation reaction [4] has been suggested as being the most suitable for the synthesis of 7-hydroxy-4-methylcoumarin because of its utilisation of cheap and easily available starting materials [3] and because of the fact that it generates coumarins substituted on the pyran ring, of which 7-hydroxy-4-methylcoumarin is among such coumarins [5]. A plethora of catalysts have been applied in this reaction with the conventional ones being mineral acids including sulphuric acid [6]. Due to known hazards presented by the use of such acid catalysts, the development of novel and greener catalysts for the reaction is necessary.

Ionic liquids, or low temperature-melting salts, are a class of compounds that have been gaining attention at an exponential rate in recent years [7]. Although considered as “neoteric” solvents [8] for organic synthetic reactions, these liquids have grown to gain widespread applications in as diverse areas as space physics [9], biotechnology [10], pharmaceutical technology [11], polymer science [12] and catalysis [13]. In catalysis, ionic liquids have been used in a dual fashion as both solvents and catalysts and as catalysts on their own with great results [7, 14].

Among the catalysts that have been studied for possible replacement of mineral acids in the Pechmann-Duisberg condensation for the production of 7-hydroxy-4-methylcoumarin and other coumarin derivatives are ionic liquids catalysts [6]. Particular and relatively great focus has been paid to ionic liquids comprising “traditional” cations and anions in this respect [15-17] but so little has been paid to other possible combinations of cations and anions [18].

The study reported in this thesis was an exploration into the use of several acidic ionic liquids to efficiently catalyze the Pechmann-Duisberg condensation reaction to produce 7-

hydroxy-4-methylcoumarin in significant yields. Specifically, N-methyl-2-pyrrolidonium hydrogen sulphate, 1-methylpyrrolidonium hydrogen sulphate and polyvinylpyrrolidonium hydrogen sulphate were applied in the reaction and their performance was compared to that of H_2SO_4 as applied via a standard organic synthetic method. While the use of these ionic liquids does not entirely eliminate the use of H_2SO_4 from the entire workup, it reduces its quantities to extremely low levels and provides a means by which recyclability can be achieved in the process. Apart from the comparison of these catalysts' performance in the reaction, their "green-ness" in the reactions was also briefly assessed as compared to that of H_2SO_4.

This chapter is broken down into four sections. The first section will provide a brief overview of ionic liquids literature; the second will discuss 7-hydroxy-methylcoumarin; the third, the Pechmann-Duisburg condensation reaction literature; and the last section will be dedicated to the formal presentation of the aims and objectives of the study.

1.1 Ionic liquids

1.1.1 Introduction

The simplest definition of ionic liquids is that they are liquids that are entirely composed of ions or are simply pure ionic compounds in liquid state. Alternatively, they may be defined as molten salts. Nearly all sources pertaining them define them more narrowly as salts that melt below 100^{o}C. It has been remarked that this temperature is arbitrary [14] although it is considered useful for both historical and practical reasons in ionic liquid research [19]. Perhaps stemming from the latter definition, ionic liquids have synonymously been referred to as room temperature ionic liquids (RTILs) [20]. Other synonyms of ionic liquids in this vein include room temperature molten salts and ambient temperature molten salts [19]. This is a reflection of the general trend in ionic liquid research where interest seems to be centred on ionic liquids that melt at or below room or ambient temperature for their ease of handling among other useful properties. Whichever definition or name one chooses to ascribe to ionic liquids, the two essential properties pertinent to their understanding and utility are their existence in pure ionic liquid state and their extremely low melting points. A succinct and objective analysis of what substances should be considered to be ionic liquids can be found in Johnson's "What are ionic liquids?" [21]. The discussion of ionic liquids in this paper will use the definition of ionic liquids as liquids composed entirely of ions and whose melting points lie below the arbitrary temperature 100^{o}C. This is to make it easier to review ionic liquids literature which almost entirely uses the latter definition in its discussions and in the research involved.

This section briefly reviews the fundamental properties of ionic liquids that have made them, and continue to make them, so attractive (See **Figure 1.1** for example) for organic synthesis and catalysis. In doing so, some common classifications of ionic liquids will be presented, noted advantages and limitations of ionic liquids will be highlighted, and their applications, with a focus on catalysis, will briefly be reviewed.

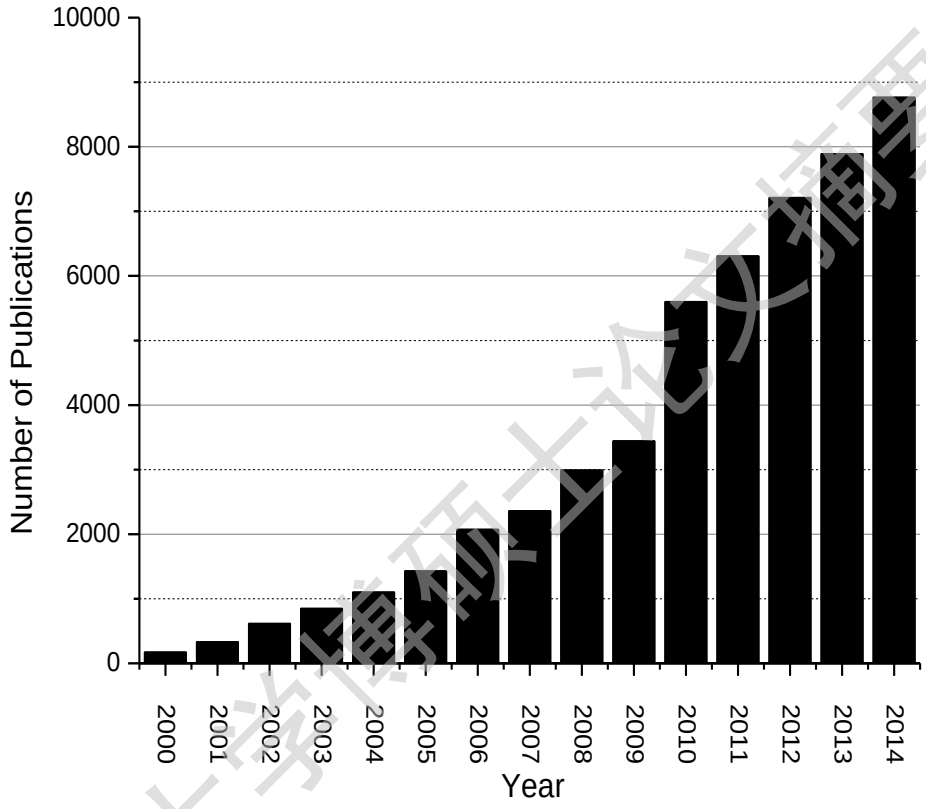

Figure 1.1 Number of publications mentioning "ionic liquid" or "ionic liquids" from the year 2000 to 2014 as searched in Web of Science.

1.1.2 Ionic liquid structures and properties

Ionic liquids, as are currently understood, are mainly composed of organic cations (commonly containing nitrogen or phosphorus) and anions that may be organic or inorganic [22]. As has already been alluded to in the previous section, the systematic classification and characterization of ionic liquids has proven to be difficult due to their diversity in structure and properties. However, several tendencies among most ionic liquids are rather obvious. For example, it is known that the physicochemical properties of ionic liquids may be altered by changing the identity and structure of their cations and anions [23, 24]. This has rendered ionic liquids

amenable to design and customization to tune their properties to suit specific applications they are intended for. **Figure 1.2** illustrates some of the most popular and currently valuable cations and anions in ionic liquid research.

At least three criteria have been used to try to classify ionic liquids. These include: (1) the identity or type of the cation [25]; (2) the presence or absence of protons in their cations [20] and; (3) their differences in other apparent properties like their attraction to water (hydrophilicity/hydrophobicity) [26]. Based on the identity of their cations, ionic liquids have been categorized into six groups: (i) those with five-membered heterocyclic cations; (ii) those with six-membered and benzo-fused heterocyclic cations; (iii) those with ammonium, phosphonium and sulphonium based cations; (iv) those with functionalized imidazolium cations and ;(v) those with chiral cations [25].

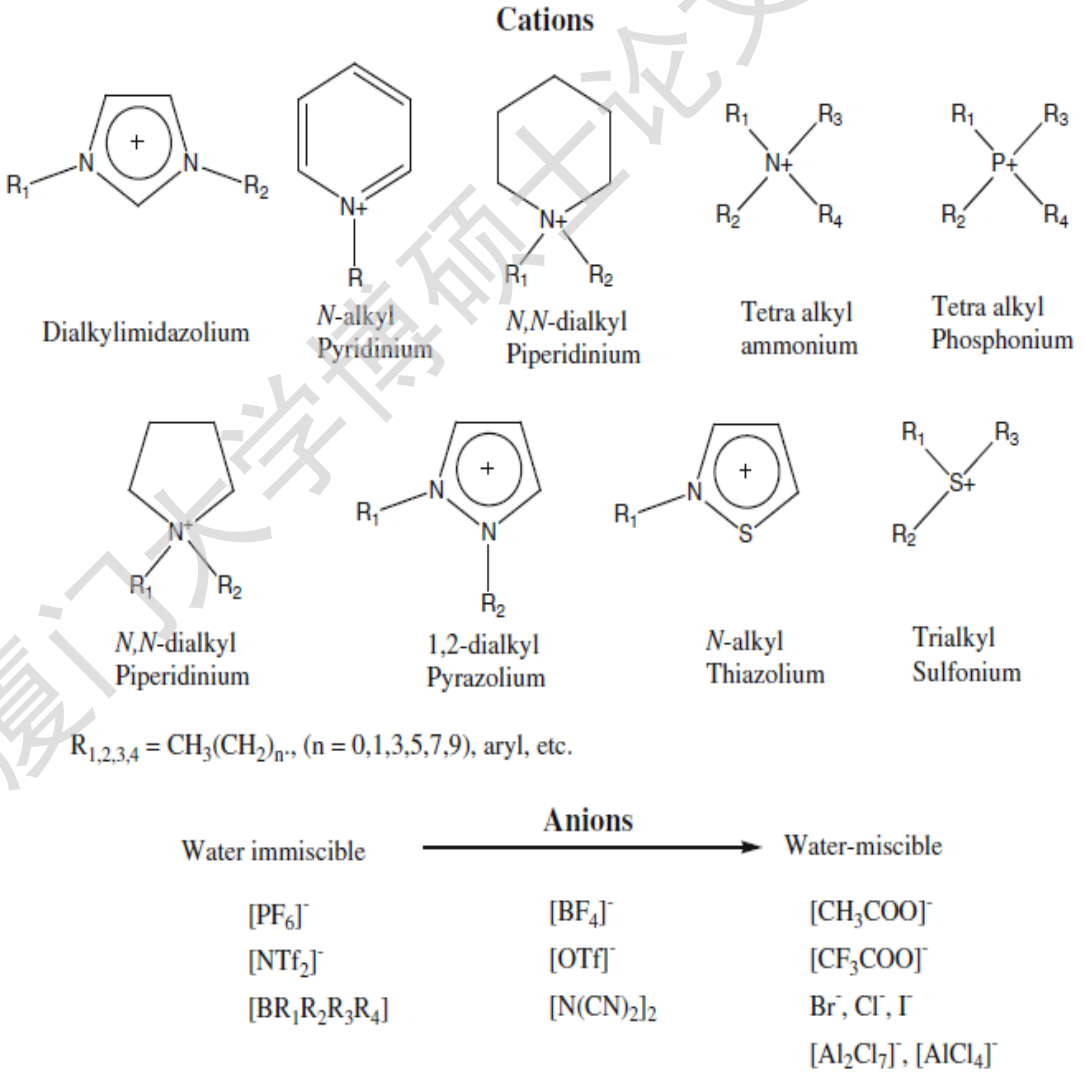

Figure 1.2 Conventionally typical ionic liquid cations and anions. Adopted from [13]